Organocatalyzed Enantioselective Synthesis of Nitroalkanes Bearing All-Carbon Quaternary Stereogenic Centers through Conjugate Addition of Acetone Cyanohydrin

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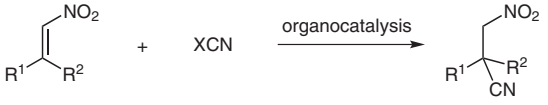
Abstract: The first organocatalyzed phase-transfer enantioselective conjugate addition of cyanide ion derived from acetone cyanohydrin to β,β′-disubstituted nitroolefins is reported. The reaction leads to the efficient formation of nitroalkanes bearing an all-carbon quaternary stereogenic center in up to 72% ee.

Key words: asymmetric synthesis, conjugate addition, cyanohydrins, organocatalysis, quaternary stereogenic center

The discovery of methods for catalytic asymmetric conjugate additions involving C-nucleophiles is an important target in synthesis[1] and nitroalkenes, being strong Michael acceptors, represent a suitable class of substrates for this reaction. Moreover the resulting nitroalkanes can be converted into highly functionalized and enantiomerically enriched organic molecules[2] that contain stereogenic centers relevant for the synthesis of biologically active compounds. To the best of our knowledge there is only one report[3] of a conjugate addition that leads to the efficient formation of an all-carbon quaternary stereogenic center by addition of an alkyl metal to a nitroalkene under metal-mediated catalysis.

The asymmetric conjugate addition of cyanide to α,β-unsaturated carbonyl derivatives, leading to very important chiral building blocks for pharmaceuticals, has been recently reported by Jacobsen[4] using a chiral aluminum salen complexes and by Shibasaki[5] and co-workers using a chiral gadolinium catalyst. Both systems employ a relatively expensive cyanide source, trimethylsilyl cyanide (TMSCN).

Herein we disclose the first method for enantioselective synthesis of nitroalkanes bearing an all-carbon quaternary stereogenic center through conjugate addition of cyanide (Scheme 1) to β,β′-disubstituted nitroolefins. Asymmetric organocatalysis, of great interest due to the conceptual importance and its environmentally benign features,[6] has been used throughout.



Scheme 1 Hydrocyanation reaction

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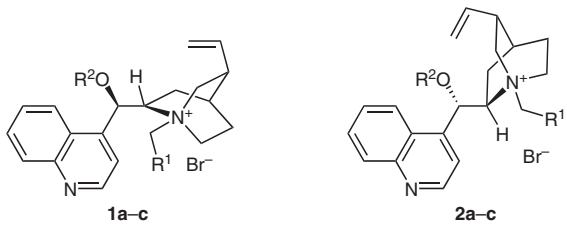


1a: R^1 = Ph, R^2 = H
1b: R^1 = Ph, R^2 = $PhCH_2$
1c: R^1 = 3,5-$CF_3C_6H_3$, R^2 = 3,5-$CF_3C_6H_3CH_2$

2a: R^1 = Ph, R^2 = H
2b: R^1 = Ph, R^2 = $PhCH_2$
2c: R^1 = 3,5-$CF_3C_6H_3$, R^2 = 3,5-$CF_3C_6H_3CH_2$

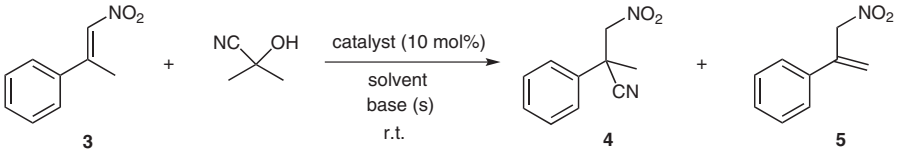
Figure 1 Structure of organocatalysts

There are a number of potentially useful methods for hydrocyanation using various cyanating agents such as hydrogen cyanide,[7] alkali or alkaline earth metal cyanides[8] and TMSCN.[9] Acetone cyanohydrin is one of the simplest, most soluble, cheap and on large scale commercially available cyanide sources.[10] Its use has been described for regiospecific epoxide opening,[11] as a Mitsunobu reagent in the cyanation of alcohols,[12] and more recently in the Strecker reaction.[13] In evaluating the various alternatives among the cyanation reagents, we were attracted to a report by Armstrong[14] that diastereoselective conjugate addition of cyanide to α,β-unsaturated oxazolidinones templates could be effected using acetone cyanohydrin and a Lewis Acid such as samarium(III) isopropoxide.

Taking into consideration the hydrogen-bond activation between the nitro group of nitroalkenes and protons of H-bond donors such as ureas and thioureas,[6] we first assumed that these derivatives[15] were probably suitable to catalyze the reaction in an enantioselective manner. Preliminary screening suggested however that these catalysts proved to be essentially inactive for the reaction, no conversion at all being typically observed after prolonged reaction time.

These results along with subsequent investigations led us to the significant conclusion that no cyanide was generated under these homogeneous conditions. Inspired by our previous findings regarding the effectiveness of acetone cyanohydrin as cyanide donor under phase-transfer conditions[13] we then turned our efforts to develop the cyanation in a biphasic system (inorganic base/organic solvent). We began our screening by examining the ability of quaternary ammonium salts derived from different cin-

Table 1 Initial Screening and Optimization of the Reaction Conditions[a]



Entry	Catalyst	Solvent	Base	Conversion (%)[b]	Yield of **4** (%)[c]	ee (%)[d]
1	**1a**	toluene	Cs_2CO_3	85	65	10
2	**2a**	toluene	Cs_2CO_3	80	70	16
3	**1b**	toluene	Cs_2CO_3	95	60	32
4	**2b**	toluene	Cs_2CO_3	95	70	40
5	**1c**	toluene	Cs_2CO_3	95	58	43
6	**2c**	toluene	Cs_2CO_3	94	70	52
7	**2b**	toluene–CH_2Cl_2	Cs_2CO_3	93	75	29
8	**2b**	(*i*-Pr)$_2$O	Cs_2CO_3	95	70	13
9	**2b**	toluene	K_2CO_3	97	72	41
10	**2c**	toluene	K_2CO_3	95	75	53
11	**2c**	toluene	K_2CO_3	94	72	67[e]

[a] Reactions were carried out with **3** (0.1 mmol), acetone cyanohydrin (18 mL, 0.2 mmol), catalyst (10 mol%) and solid base (0.2 mmol) in solvent (1 mL) at r.t. for 18 h.
[b] Determined by ^{1}H NMR spectroscopy; 8–15% of product **5** was present.
[c] Yields refer to isolated and chromatographically purified products.
[d] Determined by chiral stationary phase HPLC on an AD-H column with hexane–*i*-PrOH (80:20) as eluent, flow rate: 0.75 mL min^{-1}, t_R = 9.37 min (major), t_R = 10.40 min (minor), λ = 220 nm.
[e] Reaction was performed at –30 °C for 72 h.

chona alkaloids (Figure 1) to be effective in promoting additions to β,β′-disubstituted nitroolefins. Compound **3**[16] was employed as the test substrate.

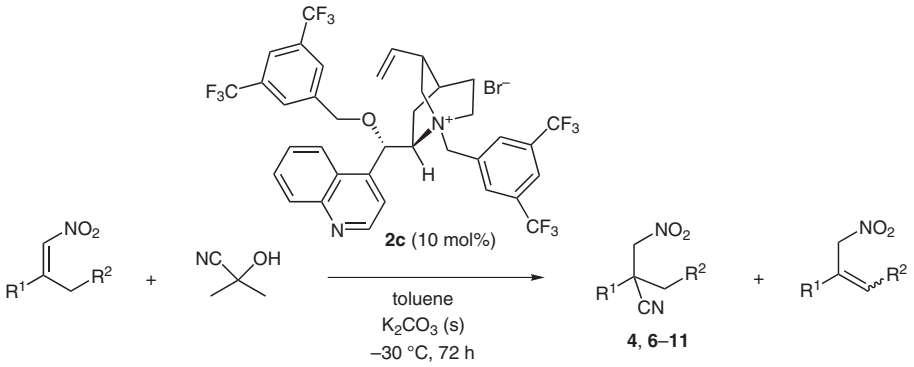
Whereas quinine and quinidine derivatives gave only racemic mixtures, more promising results were obtained (Table 1) by using cinchonidinium (**1a–c**) and cinchoninium (**2a–c**) salts, the latter leading to slightly better enantioselection (compare in Table 1 entries 1, 3 and 5 with entries 2, 4 and 6). Key elements for the success of the reaction were the protection in the organocatalyst of the free hydroxyl group at the position 9 by benzylation and the replacement of the *meta* hydrogens in these moieties by CF_3 groups.

A range of solvents was examined and toluene emerged as superior medium (better enantioselection) (compare entries 6–8). The reaction proceeded with high conversions and the expected product was isolated in fairly good yields using various mild inorganic bases such as K_2CO_3 and Cs_2CO_3. However in line with the inherent property of most β,β′-disubstituted nitroalkenes to isomerize under basic conditions or upon prolonged reaction times,[17] amounts varying up to 15% of the nonconjugated nitroalkene **5**, untouched under the reaction conditions, were found in the reaction mixture. The enantiomeric excess was not influenced by the amount of acetone cyanohydrin, whereas the chemical yields were lower using one equivalent and almost the same using five equivalents. With the aforementioned observations in hand, we set out to establish the scope[18] of the conjugated addition using **2c**[19] as the catalyst of choice. The observed beneficial effect of lowering the temperature on the enantioselectivity (Table 1, entry 11) prompted us to perform the reaction at –30 °C.

As shown in Table 2 the reactions proceeded smoothly to give the expected compounds **4** and **6–11**[20] in fairly good isolated yields and with substantial enantioselectivities. The electronic properties of the substituents on aromatic ring had a limited effect on the stereoselection of conjugate additions (entries 4–6). The size of the aliphatic group on the other hand appeared to dictate the level of enantioselectivity (entry 2) with larger groups being deleterious, whereas the opposite effect could be noticed (entry 3) on increasing the size of the aromatic moiety.

To shed some light onto the mechanism of this conjugate addition a few ancillary experiments were performed by changing also the cyanide source (Table 3). As expected no reaction occurred using KCN in the absence of catalyst (entry 1) and with acetone cyanohydrin and catalysts in the absence of base (entry 2). Interestingly (entry 3) the reaction with acetone cyanohydrin in the presence of the base led even after prolonged reaction times to very low conversion (5% ca) whereas (entry 4) by using KCN in the

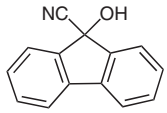
Table 2 Substrate Scope for the Organocatalytic Asymmetric Hydrocyanation of β,β′-Disubstituted Nitroolefins[a]



Entry	R^1	R^2	Product	Yield (%)[b]	ee (%)[c]
1	Ph	H	**4**	72	67
2	Ph	Et	**6**	60	33
3	2-naphthyl	H	**7**	68	72
4	4-ClC_6H_4	H	**8**	75	64
5	4-MeC_6H_4	H	**9**	62	58
6	4-$MeOC_6H_4$	H	**10**	64	56
7	2-furyl	H	**11**	52	65

[a] Reactions were carried out with substrate (0.1 mmol), acetone cyanohydrin (18 mL, 0.2 mmol), catalyst **2c** (10 mol%) and K_2CO_3 (28 mg, 0.2 mmol) in toluene (1 mL) at –30 °C for 72 h.
[b] Yields refer to isolated and chromatographically purified products.
[c] Determined by chiral stationary phase HPLC.

Table 3 Supplementary Experiments with Different Cyanide Sources[a]

Entry	Cyanide source	Base	Catalyst	Conversion (%)[b]	ee (%)[c]
1	KCN	–	–	–	–
2		–	**2c**	–	–
3		K_2CO_3	–	5	
4	KCN	–	**2c**	95	37
5		K_2CO_3	**2c**	95	53
6		K_2CO_3	**2c**	90	32
7		K_2CO_3	**2c**	93	24

[a] Reactions were carried out with substrate (0.1 mmol), catalyst **2c** (10 mol%) and K_2CO_3 (28 mg, 0.2 mmol) in toluene (1 mL) at –30 °C for 72 h.
[b] Determined by ^1H NMR spectroscopy.
[c] Determined by chiral stationary phase HPLC.

presence of catalyst **2c**, high conversion and substantial enantioselectivity could be observed (entry 4). Finally replacing acetone cyanohydrin with more sterically hindered benzophenone and fluorenone cyanohydrins, led (entries 6 and 7) to sizeable erosion of the enantioselectivity as compared to the reaction performed under the optimized conditions (entry 5).

On these grounds a preliminary mechanistic proposal for this phase-transfer organocatalyzed conjugated addition can be envisaged which highlights the key role played by the organocatalyst in the formation of a chiral ion pair in the organic medium, with the CN ion generated by interaction of the base with the cyanohydrin. The transfer of the C-nucleophile at the conjugated position of the electrophilic nitroolefin then follows. To date any prediction regarding the nature of the chiral ion pair is highly speculative. However, the deleterious effect on the enantioselectivity caused by an increase of the steric bulk in the cyanohydrins, suggests the possibility that the catalysts might accommodate in its chiral pocket an anionic species more complex than a CN ion. Finally, considering the moderate enantioselectivities in Table 2, undoubtedly in these reactions the workability of other pathways, such as an equilibrium occurring at level of chiral ion pair leading to the conjugate addition product formation without recognition of the chiral organocatalytic species, appears likely.

In conclusion, we have accomplished the first organocatalyzed phase-transfer enantioselective conjugate addition of cyanide ion derived from acetone cyanohydrin to β,β′-disubstituted nitroolefins that leads to the efficient formation of an all-carbon quaternary stereogenic center. Ongoing studies will include the screening of other organocatalytic species aimed at improving the enantioselectivity of these reactions and their further extension to other polysubstituted Michael acceptors.

Acknowledgment

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(19) ***N*,*O*-Di[3,5-bis(trifluoromethyl)benzyl]cinchoninium bromide (2c)**: 3,5-Bis(trifluoromethyl)benzyl bromide (0.48 mL, 2.6 mmol) was added to a suspension of cinchonine (0.59 g, 2.0 mmol) in toluene (6 mL). The mixture was vigorously stirred at 90 °C for 18 h and then cooled to r.t. and filtered. The white solid obtained (0.82 g, 68%) was washed with toluene (2 × 25 mL), dried under reduced pressure and used without further purification. 3,5-Bis(trifluoromethyl)benzyl bromide (0.37 mL, 2.0 mmol) and 50% aq NaOH (53 mg, 1.33 mmol) were added to a solution of *N*-3,5-bis(trifluoromethyl)benzylcinchoninium bromide (0.4 g, 0.66 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred for 6 h at r.t. and then quenched by addition of H_2O. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was purified by chromatography on silica gel column with hexane–EtOAc–MeOH–CH_2Cl_2 (5:4:2:1) as eluent to give the title product as a pale yellow solid (0.32 g, 58%); mp 162–165 °C; $[\alpha]_D^{20}$ +48.3 (*c* = 0.94, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (br s, 1 H), 8.74 (d, *J* = 7.4 Hz, 1 H), 8.37 (s, 2 H), 8.06 (s, 2 H), 7.90 (s, 2 H), 7.81 (s, 1 H), 7.54 (t, *J* = 7.05 Hz, 2 H), 7.43 (m, 1 H), 6.76 (br s, 1 H), 6.60 (d, *J* = 12.3 Hz, 1 H), 5.80 (m, 1 H), 5.53 (d, *J* = 12.4 Hz, 1 H), 5.23 (d, *J* = 10.5 Hz, 2 H), 5.04 (d, *J* = 17.0 Hz, 2 H), 4.82 (d, *J* = 12.4 Hz, 1 H), 4.65 (br s, 1 H), 4.15 (t, *J* = 10.0 Hz, 1 H), 3.29 (t, *J* = 11.0 Hz, 1 H), 2.65 (m, 1 H), 2.49 (m, 3 H), 1.84 (m, 2 H), 1.49 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.2, 148.5, 139.4, 139.3, 139.0, 134.5, 134.05, 132.4 (q, *J* = 34 Hz), 130.0, 129.9, 128.8, 127.8, 127.5, 123.05 (q, *J* = 273 Hz, CF_3), 124.9, 124.4, 122.5 (q, *J* = 273 Hz, CF_3), 122.4, 118.4, 75.1, 69.9, 66.8, 60.9, 56.0, 55.0, 37.3, 26.8, 23.4, 22.1. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 62.9 (s, 6 F), –63.0 (s, 6 F). IR ($CHCl_3$): 3367, 3030, 2960, 1371, 1278, 1176, 1142, 903 cm^{-1}. ESI–MS (+): *m*/*z* = 779 [M$^+$]. ESI–MS (–): *m*/*z* = 81, 79 [M$^-$]. Anal. Calcd for $C_{37}H_{31}BrF_{12}N_2O$: C, 53.70; H, 3.78; N, 3.39. Found: C, 53.74; H, 3.72; N, 3.44.

(20) **General Procedure for the Hydrocyanation of β,β′-Disubstituted Nitroolefins**: Catalyst (8.3 mg, 0.01 mmol) was added to a screw-tapped test tube that contained a mixture of nitroolefin (0.1 mmol), acetone cyanohydrin (0.018 mL, 0.2 mmol) and toluene (1 mL). After the resulting mixture had been cooled to –30 °C finely powdered K_2CO_3 (28 mg, 0.2 mmol) was added in one portion. The reaction mixture was then vigorously stirred at the same temperature without any precaution to exclude moisture or air. After 72 h, the reaction product was directly isolated by

column chromatography on silica gel with hexane–EtOAc (5:1) as eluent.

2-Methyl-3-nitro-2-phenylpropanenitrile: HPLC on an AD-H column with hexane–*i*-PrOH (80:20) as eluent, flow rate: 0.75 mL min^{-1}, t_R = 9.37 min (major), t_R = 10.40 min (minor), λ = 220 nm; $[\alpha]_D^{20}$ +12.4 (*c* = 0.45, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.53 (m, 5 H), 4.78 (d, *J* = 13.0 Hz, 1 H), 4.72 (d, *J* = 13.0 Hz, 1 H), 1.90 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 135.0, 129.6, 129.3, 125.5, 119.95, 81.6, 41.3, 24.8. IR ($CHCl_3$): 3021, 2928, 2855, 2248, 1562, 1449, 1374, 780, 700 cm^{-1}. ESI–MS (+): *m*/*z* = 213 [M^+ + Na].

2-Methyl-2-(naphthalen-2-yl)-3-nitropropanenitrile: HPLC on an AD-H column with hexane–*i*-PrOH (95:5) as eluent, flow rate: 0.50 mL min^{-1}, t_R = 52.59 min (minor), t_R = 54.75 min (major), λ = 254 nm; $[\alpha]_D^{20}$ +11.6 (*c* = 0.59, $CHCl_3$); mp 133–135 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 2.2 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 1 H), 7.87 (m, 2 H), 7.57 (m, 2 H), 7.51 (dd, J_1 = 8.7 Hz, J_2 = 2.2 Hz, 1 H), 4.89 (d, *J* = 13.0 Hz, 1 H), 4.81 (d, *J* = 13.0 Hz, 1 H), 1.99 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 133.13, 133.07, 132.1, 129.75, 128.3, 127.7, 127.4, 127.3, 125.6, 122.0, 120.0, 81.45, 41.5, 24.8. IR ($CHCl_3$): 3036, 2927, 2248, 1563, 1373 cm^{-1}. ESI–MS (+): *m*/*z* = 263 [M^+ + Na].

2-(4-Chlorophenyl)-2-methyl-3-nitropropanenitrile: HPLC on an AD-H column with hexane–*i*-PrOH (80:20) as eluent, flow rate: 0.75 mL min^{-1}, t_R = 10.63 min (minor), t_R = 11.85 min (major), λ = 220 nm; $[\alpha]_D^{20}$ –16.7 (*c* = 0.65, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 4 H), 4.74 (s, 2 H), 1.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 133.5, 129.7, 126.9, 119.5, 81.2, 40.9, 24.9. IR ($CHCl_3$): 3054, 2927, 2248, 1564, 1495, 1374, 1103, 1014, 815 cm^{-1}. ESI–MS (+): *m*/*z* = 247 [M^+ + Na].